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**High sensitivity C-Reactive Protein in Chronic Heart Failure:
Patient Characteristics, Phenotypes and Mode of Death**

Short title:- HsCRP in Heart Failure

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Abstract

Aims: Plasma concentrations of high sensitivity C-reactive protein (hsCRP) are often raised in chronic heart failure (CHF) and might indicate inflammatory processes that could be a therapeutic target. We aimed to study the associations between hsCRP, mode and cause of death in patients with CHF.

Methods and Results: We enrolled 4,423 patients referred to a heart failure clinic serving a local population. CHF was defined as relevant symptoms or signs with **either** a reduced left ventricular ejection fraction (LVEF) <40% **or** raised plasma concentrations of amino-terminal pro-B type natriuretic peptide (NT-proBNP >125 pg/ml).

The median (IQR) plasma hsCRP for patients diagnosed with CHF (n = 3,756) was 3.9 (1.6-8.5) mg/L and 2.7 (1.3-5.1) mg/L for those who were not (n=667; p<0.001). Patients with hsCRP \geq 10 mg/L (N=809; 22%) were older and more congested than those with hsCRP <2 mg/L (N=1,117, 30%).

During a median follow up of 53 (IQR: 28-93) months, 1,784 (48%) patients with CHF died. Higher plasma hsCRP was associated with greater mortality, independent of age, symptom severity, creatinine and NT-proBNP. Comparing a hsCRP \geq 10mg/L to <2mg/L, the hazard ratio for all-cause mortality was 2.49 (95% confidence interval: 2.19-2.84); P<0.001), for cardiovascular (CV) mortality was 2.26 (1.91-2.68; p<0.001) and for non-CV mortality was 2.96 (2.40-3.65; p<0.001).

Conclusions: In patients with CHF, a raised plasma hsCRP is associated with more congestion and a worse prognosis. The proportion of deaths that are non-CV also increases with higher hsCRP.

Key words: heart failure, CRP, inflammation, mortality, prognosis.

Introduction

Markers of inflammation, such as plasma high sensitivity C-reactive protein (hsCRP), are often elevated in patients with heart failure. Inflammation might be the primary cause of some cases of heart failure and/or contribute to its progression in many others (1-3); importantly, it might also be a therapeutic target (4, 5).

In the Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), amongst apparently healthy men and women with a low density lipoprotein cholesterol $<3.4\text{mmol/L}$ and an hsCRP $\geq 2.0\text{ mg/L}$, rosuvastatin 20 mg/day nearly halved the rate of first heart attack, stroke or cardiovascular death compared to placebo (6). In a post-hoc analysis of The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA), patients with ischaemic heart disease and reduced left ventricular ejection fraction (HFrEF) assigned to rosuvastatin 10mg/day rather than placebo had fewer cardiovascular events and a lower mortality if hsCRP was $\geq 2\text{mg/L}$ but not below this concentration (7). In The Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS), canakinumab, a human monoclonal antibody targeting interleukin-1 β , reduced the incidence of cardiovascular events and lung cancer when compared to placebo in patients with a history of myocardial infarction whose hsCRP was $\geq 2\text{ mg/L}$ (8, 9). In each of these three trials treatment reduced plasma concentrations of hsCRP compared to placebo. Medicines known to improve outcomes in patients with HFrEF, such as beta-blockers and inhibitors of the renin-angiotensin system, may also reduce plasma CRP concentrations (10).

These data suggest that hsCRP may identify patients who might respond differently to treatment, possibly because they have an inflammatory component to disease progression.

High plasma concentrations of hsCRP are also associated with adverse outcomes in chronic heart failure and could be used as an inclusion criterion to identify patients at greater risk as well as a potential therapeutic target. However, little is known about the associations between hsCRP and *mode* of death, which could influence either strategy. We now explore these issues in a large out-patient cohort.

Methods

Study Population

Between 2002 and 2015, patients with suspected or confirmed heart failure referred from both primary and secondary care physicians were enrolled at a single heart failure clinic serving a local population of about 500,000 people (The Hull LifeLab). Patients were consented for the use of their medical information prior to investigation. Some patients had no prior diagnosis of heart failure and were treatment naive, therefore requiring initiation of guideline-recommended therapy; others had a pre-existing diagnosis of heart failure and had already been initiated on treatment that might, however, require optimisation.

Information on demography, symptoms & signs, haematology and biochemistry profiles (including amino-terminal pro-B-type natriuretic peptide (NT-proBNP)), electrocardiograms (ECGs) and echocardiograms were systematically recorded in a dedicated electronic health record stored on a secure NHS server. HsCRP was routinely measured during the same visit.

This specific research question was developed post-hoc. However, data were collected prospectively for the purpose of analyses such as this. Heart failure was defined as signs or symptoms, confirmed by echocardiographic evidence of significant left ventricular systolic

dysfunction (LVSD) or abnormal NT-proBNP levels (>125 ng/L), according to current European Society of Cardiology (ESC)-HF guidelines (11). For the 2,023 patients in whom it could be measured, left ventricular ejection fraction (LVEF) was $<40\%$ in 899 (HFrEF), between 40 and 49% in 380 (HFmrEF), and $\geq 50\%$ in 744 (HFpEF). In a further 1,733 patients in whom LVEF could not be calculated, LVEF by visual estimation was considered $<40\%$ in 509 (HFrEF), 40-49% in 406 (HFmrEF) and $\geq 50\%$ in 818 (HFpEF).

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by relevant ethical bodies. All participants gave their written informed consent for their data to be used for research.

Outcome

The primary outcome of interest was all-cause mortality. Our hospital is the only one in the region offering acute medical services. With patients' consent, we have access to blood results, diagnostic investigations and correspondence on the primary and secondary care electronic records. Cause and mode of death are adjudicated at regular intervals in accordance with an in-house guideline based on information available from the clinical and electronic records (supplementary material - Adjudication process).

Statistical methods

Categorical data are presented as number and percentages; normally distributed continuous data as mean \pm SD and non-normally distributed continuous variables as median and interquartile range.

One-way ANOVA and Kruskal-Wallis tests were used to compare continuous variables between groups depending on the normality of the distribution, and the chi-squared test was used for categorical variables.

Associations between variables and prognosis were assessed using Cox proportional hazards models; variables that were significantly ($P < 0.1$) associated with mortality in univariable analysis were entered into the multivariable analysis if available in $>95\%$ of cases. Missing data were not imputed. Assumptions of the models were tested, including multicollinearity and proportional hazards.

We prospectively selected variables routinely available in clinic and known to be associated with outcome (age, sex, body mass index, systolic blood pressure, history of type II diabetes, ischaemic heart disease, NYHA IV/III (vs I/II), atrial fibrillation (vs sinus rhythm) and creatinine) to create two baseline models (with and without NT-proBNP). We measured the incremental value of the hsCRP (the model's cumulative discrimination) in predicting mortality at 2 years using Harrell's C statistic. The higher discriminative value associated with the net reclassification improvement (NRI) and the integrated discrimination improvement (IDI) for hsCRP were assessed at 2 years of follow-up. Kaplan-Meier curves with the log-rank statistic were used to illustrate outcome.

All analyses were performed using SPSS and Stata software. A 2-sided P value < 0.05 was considered statistically significant.

Results

Patient characteristics (table 1)

Of 4,423 patients evaluated, 3,756 fulfilled the criteria for HF (Figure 1 supplementary). For patients with HFrEF, HFmrEF, or HFpEF, the median (IQR) hsCRP was 4.2 (1.7-9.1) mg/L, 3.9 (1.6-9.0) mg/L and 3.7 (1.5-7.9) mg/L, respectively ($P=0.019$), and, in those who did not fulfil criteria for HF, 2.7 (1.3-5.1) mg/L ($P<0.001$ vs the HF phenotypes) (table 1 supplementary).

Patients with HF and $\text{hsCRP} \geq 10$ mg/L were older, had more symptoms and clinical signs of congestion, a higher plasma NT-proBNP and were more likely to receive loop diuretics and less likely to receive ACE inhibitors, beta-blockers and statins than those with $\text{hsCRP} < 2$ mg/L (table 1).

Outcome

During a median follow up of 53 (IQR: 28-93) months, 1,784 (48%) patients with HF died. In a multivariable Cox model, increasing hsCRP was independently associated with mortality (table 2). Compared to those with $\text{hsCRP} < 2$ mg/L, those with $\text{hsCRP} \geq 10$ mg/L had more than a two-fold increase in mortality (HR: 2.49 (95% CI: 2.19-2.84), $P<0.001$; HR: 2.42 (2.12-2.75), $p<0.001$ when corrected for age and sex, Figure 1). Those who had higher plasma concentrations of both NT-proBNP and hsCRP had the worst outcome (Figure 2).

Discrimination and reclassification improvement analysis

For the entire cohort of patients with HF, the baseline model without NT-proBNP yielded a c-index for all-cause mortality of 0.70, which rose to 0.72 when NT-proBNP was added ($p<0.001$). Including hsCRP led to an increase in c-statistic when added to the baseline model

with, or without, NT-proBNP for the overall population with HF (table 3) and for each phenotype, although this did not reach statistical significance for HFmrEF, perhaps due to smaller numbers. In a model including NT-proBNP, hsCRP increased the IDI and NRI for all-cause mortality at 2 years in the entire cohort and in each HF phenotype separately (Table 4).

Associations between hsCRP and mode of death in patients with HF.

Higher plasma concentrations of hsCRP were associated with greater all-cause mortality at two years (table 5). However, the increase in the rate of non-CV deaths (hazard ratio (95% confidence interval) for hsCRP ≥ 10 mg/L to < 2 mg/L: 2.96 (2.40-3.65; $p < 0.001$)) exceeded that for CV deaths (hazard ratio (95% confidence interval): 2.26 (1.91-2.68; $p < 0.001$)) with higher plasma hsCRP. Of the 125 deaths in patients with hsCRP < 2 mg/L, 71% were cardiovascular compared to 57% of the 256 deaths amongst those with hsCRP ≥ 10 mg/L. Patients with hsCRP ≥ 10 mg/L were at higher risk of death from infections (6.1%; predominantly respiratory or urinary) and cancer (6.0%: predominantly lung cancer).

When all-cause two-year mortality for each quartile of hsCRP was compared, the mortality was similar for each heart failure phenotype, but CV mortality was consistently lower amongst patients with HFpEF. This difference was especially striking for patients with an hsCRP ≥ 10 mg/L amongst whom only 44% of deaths were CV for those with HFpEF compared to 66% for HFfrEF and 62% for HFmrEF. (Table 5, table 2 supplementary, and Figure 3).

Discussion

There are three related findings from the present study. Firstly, about 70% of patients with heart failure attending a clinic have a hsCRP ≥ 2 mg/L, which is associated with a lower LVEF and more evidence of clinical congestion; secondly, raised plasma concentrations of hsCRP predict a higher all-cause mortality rate, independent of age, symptoms, measures of renal function and NT-proBNP; and thirdly, that with increasing hsCRP, the proportion of deaths due to non-cardiovascular causes increases, particularly for patients with HFpEF.

Moliner et al (12) found that more than half of patients attending a heart failure clinic had a hsCRP ≥ 2 ng/L but, in contrast to our findings, they did not find a relation to LVEF. This difference may reflect the small number of patients with HFmrEF and HFpEF in their study (n=270, 25% of the entire cohort), and differences in the criteria for diagnosing HFpEF.

A few post-hoc studies from large randomised controlled trials have shown that high levels of CRP/hsCRP are associated with adverse cardiovascular outcomes in out-patients with HFrEF, and there are similar findings from smaller registries enrolling patients with either HFrEF or HFpEF (13-15). There are some exceptions. In CORONA, hsCRP was not an independent predictor of mortality (16). In the RED-HF trial, in which patients with HFrEF and anaemia were enrolled, compared to the lowest tercile, patients in the highest tercile of hsCRP had higher mortality, but hsCRP did not improve risk stratification in models that used NT-proBNP (17). The reasons for the discrepancy include the fact that patients enrolled in randomised controlled trials are younger, and far less likely to have complex (and often multiple) co-morbidities than those enrolled in “real life” registries such as ours (18). As a consequence, patients enrolled in CORONA had a median hsCRP of 3.4 mg/L and in the patients in RED-HF who had an event, median hsCRP was 3.5 mg/l (and was only 2.2 mg/L

in those without events). In comparison, the patients with HFrEF in our study had a median hsCRP of 4.2 mg/L.

We found that including hsCRP modestly increased the discrimination and prediction of outcome models, suggesting that inflammation is related to mortality above and beyond other commonly used clinical variables, including NT-proBNP. Thus, there may be some value in exploring further inflammation and its treatment in patients with HF.

Inflammation is associated with atherosclerosis (19); and the response to acute infections can result in acute myocardial ischaemia (20). Chronic inflammatory conditions, such as rheumatoid arthritis, predispose to heart failure through both ischaemic and non-ischaemic mechanisms (21, 22), and might cause an increase in plasma concentrations of natriuretic peptides (23). Development of venous congestion further activates the innate immune system and enhances secretion of pro-inflammatory cytokines, leading to a subsequent rise in circulating hsCRP levels (24). An intriguing hypothesis for which there is increasing evidence is that heart failure causes inflammation via translocation of bacterial endotoxin through oedematous bowel wall. The resulting activation of the innate immune system leads to a rise in CRP (25). There is some evidence to suggest that CRP is itself toxic to the myocardium (26), suggesting a mechanism by which inflammation may continue to damage the heart.

To the best of our knowledge, this is the first paper describing the associations between hsCRP with *mode* of death in ambulatory patients with heart failure. Our findings are consistent with a Japanese registry enrolling patients with acute heart failure in whom CRP (and not hsCRP) was measured at admission: compared to those in the lowest tercile (<2.9

mg/L; N= 1584), patients in the highest tercile of CRP (>11.8 mg/L; n=1596) had a greater CV (19.6% v 11.7%) and non-CV (17.9% v 6.0%) mortality at 720 days, with a substantial increase in the *proportion* of deaths due to non-CV causes (from 34 to 48%) (27).

We found that patients with a raised hsCRP had a higher proportion of deaths from non-cardiovascular causes, particularly cancer. This observation was particularly striking amongst patients labelled as having HFpEF. HFpEF is often a diagnosis of exclusion, and it is less certain genuinely to represent cardiovascular disease than a diagnosis of HFrEF. In turn, it also suggests that a more advanced age and a greater number of comorbidities, rather than the extent of cardiac dysfunction, significantly contribute to the poor prognosis of patients with HFpEF. Of note, early diagnosis and therapeutic advances, such as better treatments of ischaemic heart disease and hypertension, have modified the natural history of HFpEF over the past few decades, with a large increase in the proportion of non-cardiovascular deaths in this population (28). It is also possible that many of the patients with high hsCRP who subsequently died had undetected cancer at the time of heart failure diagnosis, and an important consequence is that treatment targeted at heart failure can only have a limited effect on outcome in patients with a high hsCRP. However, cancer has long been known to be intimately involved with the immune system, and inflammation might contribute to an increased risk of developing cancer in patients with heart failure (29, 30).

Using hsCRP might be helpful in designing future clinical trials. A raised hsCRP identifies a population at higher risk of adverse outcome. This group might be particularly susceptible to treatment directed at inflammation. However, because a higher proportion of the deaths in such a group is non-cardiovascular, treatment directed specifically at heart failure might have a large effect on cardiovascular death, but a substantially lesser effect on total mortality. In

contrast, enrolling only those patients with a low hsCRP might identify a population in whom deaths are likely to be cardiovascular, but in whom the absolute death rate is low. These observations might be particularly important in patients labelled as having HFmrEF or HFpEF, in whom non-cardiovascular deaths might be more common than cardiovascular.

Limitations

We only assessed hsCRP at baseline, as it was not routinely measured in all patients during follow-up. Initiation or up-titration of guideline-recommended treatments for HFrEF might have reduced plasma concentrations of hsCRP and improved outcome. Other potential confounders, for instance time-dependent changes in medications, have not been assessed. We did not exclude patients with chronic infections or auto-immune conditions, and we cannot exclude the possibility that many patients had an occult malignancy at the time of presentation to the cardiology service.

It could be argued that in many patients in whom LVEF was not measured, visual assessment of left ventricular systolic dysfunction might have led to misclassification of HF phenotypes. The classification system tacitly assumes that echocardiography is an accurate means of measuring left ventricular ejection fraction, and that it is a stable measurement from day to day. Neither assumption is correct. In our population, it is very probable that many of the patients could have been included in a different group had their echocardiogram been reported by a different operator or repeated on a different day.

Some readers might not accept an NT-proBNP above 125 pg/ml as being diagnostic of heart failure, whether HFmrEF or HFpEF. The definition we used is, however, consistent with

recent ESC-HF guidelines (11) and the median NT-proBNP in our patients with HFpEF in sinus rhythm was higher than that amongst the patients with HFpEF and sinus rhythm enrolled in recently published trials, such as EDIFY, in which the median NT-proBNP was 375 (IQR: 253-701) ng/l as compared with 389 (IQR: 211-846) ng/l in our population (31).

Conclusions

In ambulatory patients with HF, higher plasma concentrations of hsCRP are a powerful predictor of mortality, and identify those with higher natriuretic peptides who are also more likely to die of non-cardiovascular causes.

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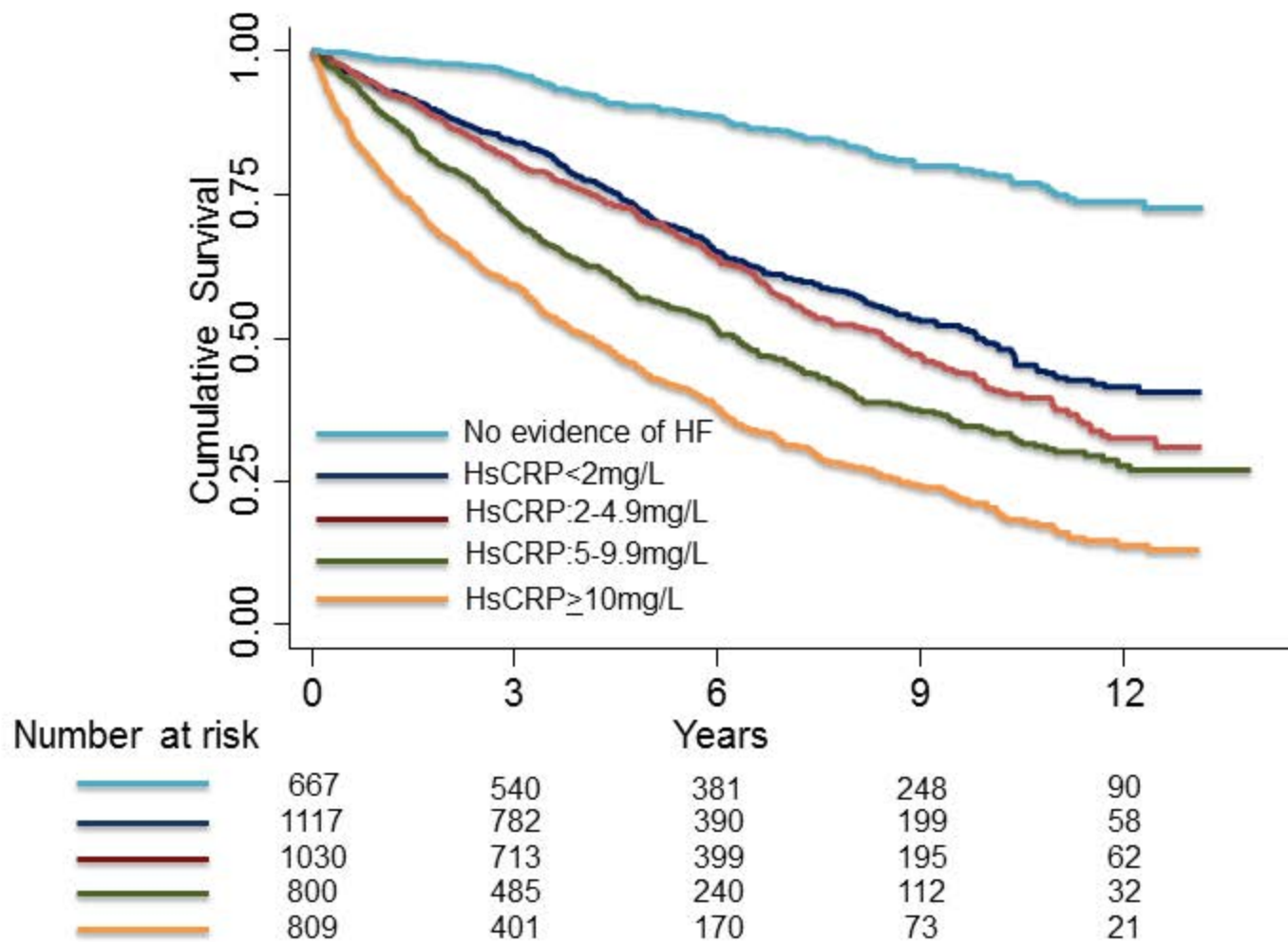
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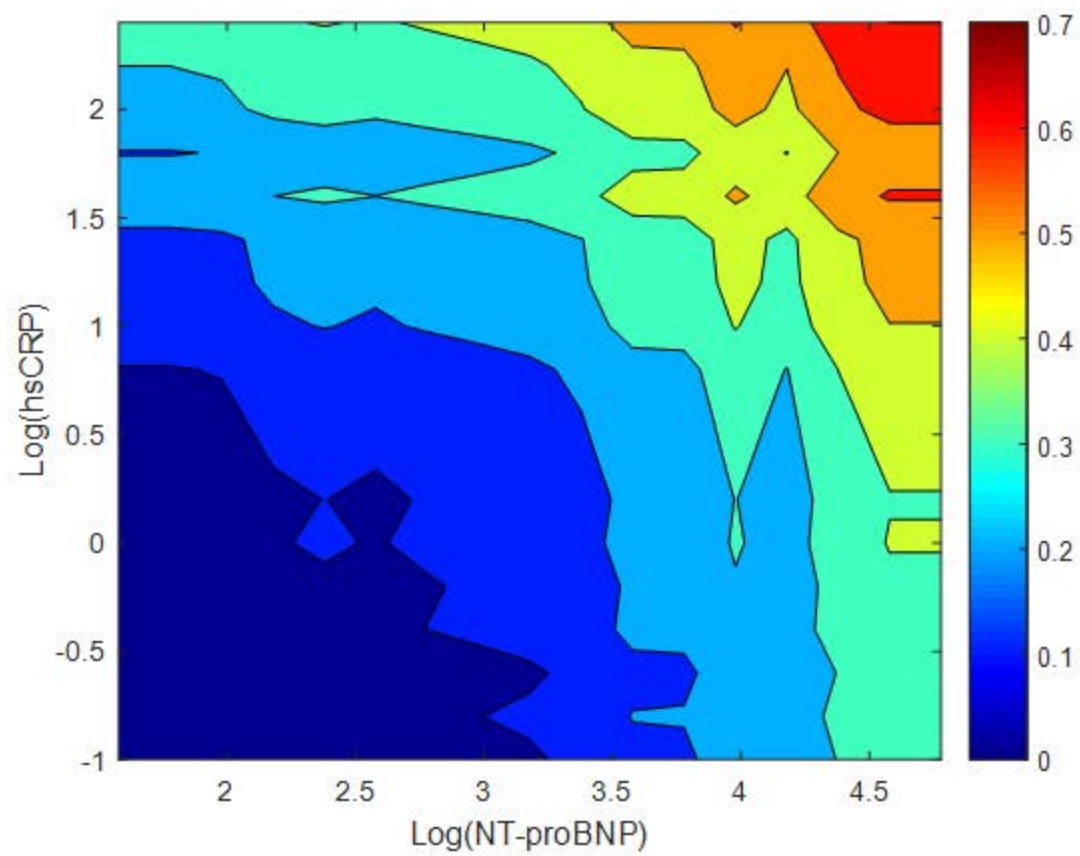
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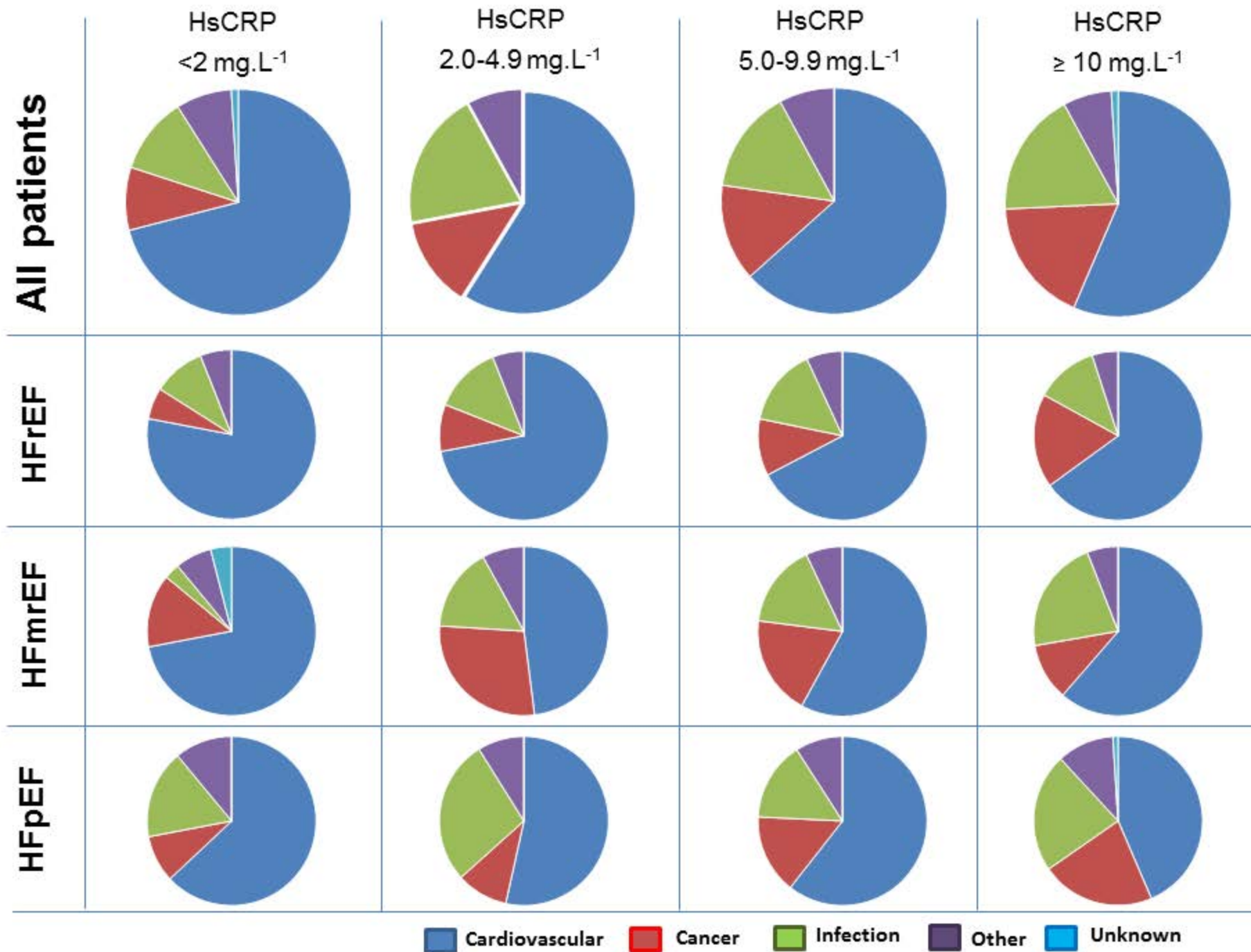
Figure 1: Kaplan Meier curve for the primary outcome of death from all causes. Compared to those with hsCRP <2mg/L, those with hsCRP \geq 10mg/L had more than a two-fold increase in mortality (HR: 2.49 (95% CI: 2.19-2.84), unadjusted; and HR: 2.42 (95% CI: 2.12-2.75) adjusted for age and sex; P<0.001 for both).

Figure 2: heat map showing the interaction between hsCRP and NT-proBNP and their relationship with probability of death at 2 years in patients with heart failure.

Figure 3: Venn diagram showing proportion of deaths at 2 years amongst all patients with HF (n=3,538, top row), or by different HF phenotypes, attributed to cardiovascular disease (in blue), cancer (red), infection (green), other (purple), on in whom the more likely cause of death was unknown (light blue).







Variable	Missing	1 st Decile of HsCRP* (n=348)	HsCRP <2 mg/L N=1117	HsCRP 2-4.9 mg/L N=1030	HsCRP 5.0-9.9 mg/L N=800	HsCRP ≥10mg/L N=809	10 th decile of hsCRP* (n=376)	P
Demographics								
Age – years	0	73 (64-79)	74 (66-80)	74 (66-80)	73 (66-80)	75 (68-81)	77 (69-82)	0.008
Sex (male) – no. (%)	0	228 (66)	722 (65)	647 (63)	470 (59)	494 (61)	248 (66)	0.06
Body mass index -kg/m ²	20	27 (5)	28 (5)	30 (6)	30 (7)	29 (7)	28 (7)	<0.001
Systolic blood pressure – mmHg	14	136 (118-153)	139 (122-156)	139 (122-158)	138 (120-157)	132 (114-153)	129 (111-153)	<0.001
Heart rate – bpm	29	67 (59-79)	68 (60-80)	71 (60-82)	74 (64-87)	78 (67-91)	80 (69-92)	<0.001
Sinus rhythm – no. (%)	48	267 (77)	839 (76)	715 (70)	540 (69)	537 (67)	257 (69)	<0.001
Peripheral oedema≥ankles – no. (%)	335	51 (16)	197 (19)	242 (26)	238 (33)	291 (40)	147 (43)	<0.001
Lung crackles – no. (%)	555	18 (6)	80 (8)	122 (14)	133 (20)	167 (24)	88 (27)	<0.001
Raised JVP – no. (%)	556	23 (8)	84 (9)	122 (14)	124 (18)	165 (24)	82 (26)	<0.001
Diabetes – no. (%)	0	87 (25)	288 (26)	257 (25)	193 (24)	213 (26)	103 (27)	0.74
h/o Hypertension – no. (%)	0	169 (49)	564 (51)	561 (55)	427 (53)	409 (51)	187 (50)	0.19
IHD – no. (%)	0	202 (59)	601 (54)	533 (52)	397 (50)	384 (48)	186 (50)	0.039
Previous or current Smokers – no. (%)	0	36 (10)	150 (13)	162 (16)	142 (18)	157 (19)	74 (20)	0.003
COPD – no. (%)	0	13 (4)	69 (6)	79 (8)	90 (11)	108 (13)	56 (15)	<0.001
HFrEF – no. (%)	0	127 (37)	401 (36)	364 (35)	322 (40)	321 (40)	153 (41)	0.10
HFmrEF– no. (%)		67 (19)	231 (21)	212 (21)	166 (21)	177 (22)	94 (25)	
HFpEF– no. (%)		154 (44)	485 (43)	454 (44)	312 (39)	311 (38)	129 (34)	
NYHA Class I – no. (%)	12	115 (33)	318 (29)	236 (23)	111 (14)	87 (11)	37 (10)	<0.001
NYHA Class II – no. (%)		169 (49)	551 (50)	496 (48)	392 (49)	346 (43)	155 (41)	
NYHA Class III – no. (%)		63 (18)	240 (21)	284 (28)	274 (34)	339 (42)	158 (42)	
NYHA Class IV – no. (%)		0 (0)	5 (<1)	11 (1)	20 (3)	34 (4)	25 (7)	
Blood results								
NT-proBNP – ng/L	220	727 (272-1573)	803 (322-1781)	904 (364-2086)	1073 (411-2704)	1612 (659-4067)	2156 (779-5663)	<0.001
NT-proBNP in SR – ng/l	158	495 (228-1247)	566 (261-1328)	628 (267-1517)	737 (286-2118)	1197 (473-3160)	1418 (605-4117)	<0.001
NT-proBNP in AF – ng/l	57	1428	1496	1682	1861	2613	3919	<0.001

		(989-2544)	(1027-2609)	(996-2895)	(996-3419)	(1175-5444)	(1980-6670)	
HsCRP – mg/L	0	0.4 (0.3-0.5)	1.0 (0.6-1.4)	3.2 (2.5-4.0)	6.8 (5.8-8.1)	19.0 (13.0-35.0)	37.0 (27.0-59.0)	NA
HsCRP - range	0	0.1-0.6	0.1-1.9	2.0-4.9	5.0-9.9	10.0-299	21-299	NA
Haemoglobin – g/L	202	13.6 (1.6)	13.5 (1.6)	13.5 (1.7)	13.3 (1.7)	12.5 (1.9)	12.2 (1.8)	<0.001
White cell count - 10⁹.L⁻¹	195	6.6 (5.5-7.8)	6.6 (5.6-8.0)	7.1 (6.0-8.4)	7.5 (6.2-8.7)	8.0 (6.6-9.7)	8.3 (6.7-10.3)	<0.001
Neutrophils- 10⁹.L⁻¹	551	4.0 (3.3-4.8)	4.1 (3.3-5.0)	4.4 (3.6-5.5)	4.8 (3.8-5.8)	5.4 (4.3-6.7)	5.7 (4.6-7.3)	<0.001
Lymphocytes - 10⁹.L⁻¹	551	1.7 (1.4-2.1)	1.7 (1.3-2.2)	1.7 (1.3-2.2)	1.7 (1.2-2.1)	1.5 (1.1-2.0)	1.4 (1.0-1.8)	<0.001
Plasma viscosity - mPaSec	984	1.6 (0.1)	1.6 (0.1)	1.7 (0.1)	1.7 (0.2)	1.8 (0.2)	1.9 (0.2)	<0.001
Creatinine-μmol/L	85	93 (80-113)	94 (80-116)	99 (82-119)	101 (81-129)	107 (86-141)	115 (88-150)	<0.001
Urea - mmol/L	89	6.3 (5.2-8.2)	6.4 (5.1-8.4)	6.6 (5.1-8.9)	6.9 (5.2-9.6)	7.7 (5.6-11.1)	8.0 (5.8-11.9)	<0.001
Albumin – g/L	104	40 (3)	39 (3)	38 (3)	37 (3)	34 (4)	33 (4)	<0.001
Cholesterol -mmol/L	208	4.4 (1.2)	4.5 (1.2)	4.6 (1.2)	4.7 (1.4)	4.4 (1.2)	4.6 (1.3)	<0.001
Bilirubin – μmol/L	105	15 (12-18)	14 (12-18)	14 (12-18)	14 (11-18)	13 (11-18)	13 (10-18)	<0.001
ALP - iu/L	95	64 (52-76)	66 (54-80)	71 (58-88)	78 (63-96)	86 (69-111)	88 (71-114)	<0.001
ALT - iu/L	97	21 (17-27)	21 (17-27)	21 (17-27)	19 (15-26)	19 (15-26)	18 (14-26)	<0.001
#Medications								
Loop diuretic – no (%)	0	169 (49)	594 (53)	655 (64)	536 (67)	604 (75)	285 (76)	<0.001
Mineralocorticoid antagonists– no (%)	0	82 (24)	241 (22)	194 (19)	164 (21)	177 (22)	80 (21)	0.33
ACE-I or ARB– no (%)	0	258 (74)	796 (71)	767 (75)	539 (67)	543 (67)	231 (61)	0.001
Beta-blockers– no (%)	0	222 (64)	710 (64)	635 (62)	432 (54)	434 (54)	198 (53)	<0.001
Statins – no.%	0	231 (66)	720 (64)	576 (56)	388 (49)	355 (44)	166 (44)	<0.001
Echocardiography								
##LVEF (when measured) - %	1733	46 (32-56)	45 (34-56)	42 (33-56)	40 (30-55)	40 (30-55)	39 (30-50)	<0.001
LAD - cm	436	4.1 (0.8)	4.1 (0.8)	4.2 (0.8)	4.3 (0.8)	4.2 (0.8)	4.2 (0.8)	0.003

Table 1 – Characteristics of patients with HF (n = 3,756) stratified by plasma concentration of HsCRP. *Patients in the lowest decile are a subset of those in the lowest quartile (counted in both). *Patients in the highest decile are a subset of those in the highest quartile (counted in both). # Medications recorded at baseline prior to changes subsequent to initial referral ## LVEF was measured in 2,023 patients (54%) and was visually estimated in the remainder as <40%, 40-49% or ≥50%. Abbreviations used: JVP – jugular venous pressure; IHD – ischaemic heart

disease; HFrEF - heart failure with reduced ejection fraction; HFmrEF - heart failure with midrange ejection fraction; HFpEF - heart failure with preserved ejection fraction; SR – sinus rhythm; AF – atrial fibrillation; ALT - alanine aminotransferase; ALP - alkaline phosphatase; LVEF – left ventricular ejection fraction; LAD – left atrial diameter.

	Univariable analysis			Multivariable analysis		
Variable	HR (95% CI)	χ^2	p-value	HR (95% CI)	χ^2	p-value
Age - years	1.05 (1.05-1.06)	364	<0.001	1.05 (1.04-1.05)	185	<0.001
Sex (male) - no. (%)	1.15 (1.05-1.27)	8	0.005	1.31 (1.16-1.47)	20	<0.001
Body mass index -kg/m ²	0.97 (0.96-0.97)	62	<0.001	0.99 (0.98-1.00)	7	0.009
Systolic blood pressure – mmHg	0.99 (0.99-1.00)	46	<0.001	0.99 (0.99-1.00)	8	0.005
Heart rate – bpm	1.01 (1.00-1.01)	32	<0.001			
AF – (Yes vs no)	1.34 (1.21-1.48)	31	<0.001			
Peripheral oedema (≥ankles vs <)	1.78 (1.61-1.98)	116	<0.001			
Lung crackles – (Yes vs no)	1.93 (1.70-2.19)	106	<0.001			
Raised JVP – (Yes vs no)	1.96 (1.73-2.23)	107	<0.001			
Diabetes - (Yes vs no)	1.17 (1.05-1.31)	8	0.005			
Hypertension - (Yes vs no)	0.99 (0.90-1.09)	0	0.89			
IHD - (Yes vs no)	1.13 (1.02-1.24)	6	0.014			
Previous or current Smokers – no. (%)	1.08 (0.96-1.23)	2	0.20			
HFrEF (vs other phenotypes)	1.25 (1.14-1.37)	22	<0.001			
HFrEF (vs HFpEF)	1.31 (1.18-1.45)	26	<0.001			
HFrEF (vs HFmrEF)	1.16 (1.03-1.31)	6	0.018			
HFmrEF (vs HFpEF)	1.13 (0.89-1.28)	3	0.073			
NYHA Class IV/III vs I/II	2.05 (1.86-2.25)	215	<0.001	1.54 (1.37-1.72)	55	<0.001
LogNTproBNP	2.89 (2.64-3.17)	507	<0.001	1.71 (1.51-1.95)	68	<0.001
LogHsCRP	1.85 (1.70-2.02)	207	<0.001	1.33 (1.19-1.48)	27	<0.001
Haemoglobin – g/L	0.82 (0.80-0.84)	199	<0.001			
White cell count - 10 ⁹ .L ⁻¹	1.03 (1.02-1.04)	36	<0.001			
Neutrophils- 10 ⁹ .L ⁻¹	1.03 (1.02-1.04)	90	<0.001			
Lymphocytes - 10 ⁹ .L ⁻¹	0.89 (0.83-0.95)	11	0.001			
Plasma viscosity - mPaSec	3.87 (2.77-5.41)	63	<0.001			
Creatinine-μmol/L	1.003 (1.002-1.003)	188	<0.001			
Urea - mmol/L	1.06 (1.05-1.06)	354	<0.001	1.02 (1.01-1.03)	24	<0.001
Albumin – g/L	0.89 (0.88-0.90)	342	<0.001	0.97 (0.95-0.99)	14	<0.001
Cholesterol -mmol/L	0.92 (0.89-0.96)	15	<0.001			
Bilirubin – μmol/L	1.01 (1.00-1.01)	22	<0.001			

ALP - iu/L	1.01 (1.00-1.01)	223	<0.001	1.003 (1.002-1.004)	27	<0.001
ALT - iu/L	0.99 (0.98-0.99)	18	<0.001			
LAD - cm	1.27 (1.19-1.35)	57	<0.001			

Table 2 – Univariable and multivariable *Cox* proportional hazard *models* for all-cause mortality in patients with heart failure. Variables entered in the multivariable model are highlighted in bold. Abbreviations used: JVP – jugular venous pressure; IHD – ischaemic heart disease; HFrEF - heart failure with reduced ejection fraction; HFmrEF - heart failure with midrange ejection fraction; HFpEF - heart failure with preserved ejection fraction; AF – atrial fibrillation; ALT - alanine aminotransferase; ALP - alkaline phosphatase; LVEF – left ventricular ejection fraction; LAD – left atrial diameter.

Model comparison	C-index	Δ C-index (by adding log(hsCRP))	Compared to model 1/model M2 (t-statistic, p-value)
Model 1			
All HF Patients (n =3,413)	0.70	0.02	t=4.17, p<0.0001
HFrEF (n =1,157)	0.69	0.02	<i>t=2.80, p=0.005</i>
HFmrEF (n =764)	0.72	0.01	<i>t=1.35, p=0.18</i>
HFpEF (n =1,492)	0.70	0.03	<i>t=3.08, p=0.002</i>
Model 2			
All HF Patients (n =3,413)	0.72	0.02	t=3.86, p<0.0001
HFrEF (n =1,157)	0.73	0.01	<i>t=1.95, p=0.05</i>
HFmrEF (n =764)	0.73	0.01	<i>t=1.49, p=0.14</i>
HFpEF (n =1,492)	0.74	0.02	<i>t=3.08, p=0.002</i>

Table 3: Model discrimination.*Model 1: Age, Sex, BMI, SBP, DM, IHD, NYHA IV/III vs I/II, AF and creatinine. **Model 2: model M1 + log(NT-proBNP). Results are shown in bold for all patients and in *Italic* for each HF phenotype. Abbreviations used: HFrEF - heart failure with reduced ejection fraction; HFmrEF - heart failure with midrange ejection fraction; HFpEF - heart failure with preserved ejection fraction.

<i>All HF patients (n=3,413)#</i>				
Model comparison	cNRI (95%CI)	p-value	IDI (95%CI)	p-value
Model 1 + log(hsCRP)	0.36 (0.27-0.45)	<0.0001	0.021 (0.015-0.027)	<0.0001
Model 2 + log(hsCRP)	0.30 (0.21-0.39)	<0.0001	0.013 (0.007-0.0189)	<0.0001
<i>HF_rEF population (n=1,157)</i>				
Model 1 + log(hsCRP)	0.36 (0.20-0.52)	<0.0001	0.019 (0.009-0.029)	0.0003
Model 2 + log(hsCRP)	0.22 (0.06-0.38)	0.003	0.008 (0.0002-0.016)	0.031
<i>HF_{mr}EF population (764)</i>				
Model 1 + log(hsCRP)	0.38 (0.20-0.56)	<0.0001	0.016 (0.004-0.028)	0.008
Model 2 + log(hsCRP)	0.30 (0.12-0.48)	0.0013	0.010 (0.0002-0.020)	0.041
<i>HF_pEF Population (n=1,492)</i>				
Model 1 + log(hsCRP)	0.34 (0.20-0.48)	<0.0001	0.023 (0.013-0.033)	<0.0001
Model 2 + log(hsCRP)	0.30 (0.16-0.44)	<0.0001	0.015 (0.005-0.025)	0.0013

Table 4: Improvement in prediction of all-cause mortality at 2 years by using log(hsCRP). Model 1: Age, Sex, BMI, SBP, DM, IHD, NYHA IV/III vs I/II, AF and creatinine. Model 2: model 1 + log(NtproBNP). # excludes 218 patients who had follow-up shorter than 2 years or those with missing values (n=125).

Cause and mode of death at 2 years in 3,538 patients with HF, according to phenotype and hsCRP levels[#]

	HFrEF					HFmrEF					HFpEF				
	All N=1353	HsCRP <2 mg/L N=381	HsCRP 2.0-4.9 mg/L N=354	HsCRP 5.0-9.9 mg/L N=310	HsCRP ≥10 mg/L N=308	All N=743	HsCRP <2 mg/L N=221	HsCRP 2.0-4.9 mg/L N=203	HsCRP 5.0-9.9 mg/L N=156	HsCRP ≥10 mg/L N=163	All N=1442	HsCRP <2 mg/L N=455	HsCRP 2.0-4.9 mg/L N=418	HsCRP 5.0-9.9 mg/L N=286	HsCRP ≥10 mg/L N=283
2-Y mortality	20.7% (n=280)	13.1% (n=50)	13.3% (n=47)	24.2% (n=75)	35.1% (n=108)	18.8% (n=140)	13.1% (n=29)	12.3 % (n=25)	19.8% (n=31)	33.8% (n=55)	17.3% (n=250)	10.1% (n=46)	13.9% (n=58)	18.5% (n=53)	32.9% (n=93)
Cause and mode of Death															
CV	14.4% (n=195)	10.2% (n=39)	9.6% (n=34)	16.5% (n=51)	23.1% (n=71)	11.4% (n=85)	9.5% (n=21)	5.9% (n=12)	11.5% (n=18)	20.9% (n=34)	9.2% (n=133)	6.4% (n=29)	7.4% (n=31)	11.2% (n=32)	14.5% (n=41)
<i>Terminal HF</i>	5.0% (n=68)	2.9% (n=11)	3.9% (n=14)	6.5% (n=20)	7.5% (n=23)	2.4% (n=18)	2.7% (n=6)	0.5% (n=1)	3.2% (n=5)	3.7% (n=6)	2.5% (n=36)	1.8% (n=8)	1.2% (n=5)	3.1% (n=9)	4.9% (n=14)
<i>Sudden</i>	8.2% (n=112)	6.3% (n=24)	5.1% (n=18)	8.4% (n=26)	14.3 % (n=44)	7.1% (n=53)	5.4% (n=12)	4.9% (n=10)	7.7% (n=12)	11.7% (n=19)	5.3% (n=76)	3.7% (n=17)	4.5% (n=19)	6.3% (n=18)	7.8% (n=22)
<i>Other CV</i>	1.2% (n=15)	1.0% (n=4)	0.6% (n=2)	1.6% (n=5)	1.3% (n=4)	1.9% (n=14)	1.4% (n=3)	0.5% (n=1)	0.6% (n=1)	5.5% (n=9)	1.4% (n=21)	0.9% (n=4)	1.7% (n=7)	1.8% (n=5)	1.8% (n=5)
Non-CV	6.3% (n=85)	2.9% (n=11)	3.7% (n=13)	7.7% (n=24)	12.0% (n=37)	7.4% (n=55)	3.6% (n=8)	6.4% (n=13)	8.3% (n=13)	12.9% (n=21)	8.1% (n=117)	3.7% (n=17)	6.5% (n=27)	7.3% (n=21)	18.4% (n=52)
<i>Infection</i>	2.6% (n=35)	1.3% (n=5)	1.7% (n=6)	3.5% (n=11)	4.2% (n=13)	3.0% (n=22)	0.5% (n=1)	2.0% (n=4)	3.2% (n=5)	7.4% (n=12)	3.7% (n=53)	1.7% (n=8)	3.8% (n=16)	2.8% (n=8)	7.4% (n=21)
<i>Cancer</i>	2.5% (n=34)	0.8% (n=3)	1.1% (n=4)	2.6% (n=8)	6.2% (n=19)	3.1% (n=23)	1.8% (n=4)	3.4% (n=7)	3.8% (n=6)	3.7% (n=6)	2.6% (n=38)	0.9% (n=4)	1.5% (n=6)	2.8% (n=8)	7.1% (n=20)
<i>Other Non CV/Unknown*</i>	1.2% (n=16)	0.8% (n=3)	0.9% (n=3)	1.6% (n=5)	1.6% (n=5)	1.3% (n=10)	1.3% (n=3)	1.0% (n=2)	1.3% (n=2)	1.8% (n=3)	1.8% (n=26)	1.1% (n=5)	1.2% (n=5)	1.7% (n=5)	3.9% (n=11)
Origin of Cancer Attributed to Death															
<i>Lung</i>	13	1	3	2	7	5	1	1	1	2	13	0	3	1	9
<i>Prostate</i>	2	0	0	0	2	2	0	2	0	0	1	0	0	1	0
<i>GI</i>	5	1	0	2	2	9	3	1	3	2	9	2	3	1	3
<i>Blood</i>	4	0	0	2	2	1	0	0	1	0	5	1	0	2	2
<i>Renal/Urinary</i>	2	0	1	0	1	1	0	0	0	1	3	0	0	1	2
<i>Breast</i>	2	0	0	0	2	1	0	0	1	0	2	0	0	2	0

<i>Pancreas</i>	<i>3</i>	<i>1</i>	<i>0</i>	<i>1</i>	<i>1</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>1</i>	<i>1</i>	<i>0</i>	<i>0</i>	<i>0</i>
<i>Liver</i>	<i>1</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>1</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>1</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>1</i>
<i>Other/Unknown</i>	<i>2</i>	<i>0</i>	<i>0</i>	<i>1</i>	<i>1</i>	<i>4</i>	<i>0</i>	<i>3</i>	<i>0</i>	<i>1</i>	<i>3</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>3</i>

Table 5. Rate, cause and mode of death at 2 years (2-Y) in all patients with HF, according to different HF phenotypes and cut-offs of HsCRP. Abbreviations used: CV: cardiovascular; GI: gastrointestinal; HF: heart failure; HFrEF - heart failure with reduced ejection fraction; HFmrEF - heart failure with midrange ejection fraction; HFpEF - heart failure with preserved ejection fraction.[#] excludes 218 patients who had follow-up shorter than 2 years. * The mode and cause of death were adjudicated as “unknown” in two patients only (one with HFmrEF and one with HFpEF).